ECONOMIC ANALYSIS

commentary

Revisiting Fulvestrant Dosing in Uncertain Economic Times

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Fulvestrant, a direct estrogen receptor (ER) antagonist, was approved for hormone receptor (HR)–positive metastatic breast cancer (MBC) in 2002 at a dose of 250 mg given once every month. Subsequently, the recommended dose was changed to 500 mg once a month in 2010, and since then, it is universally used as a 500 mg intramuscular dose given once every month.[1] It is used as a second-line therapy as well as in upfront settings, either alone or in combination with small molecule-targeted agents.[2] Most guidelines continue to recommend the 500 mg dose as the standard therapy; however, the cost of providing this therapy remains a major challenge for every country. Double dose means double cost, and the question then arises whether the benefit is truly double as well? We present our viewpoint on dosing of fulvestrant in terms of efficacy in relation to cost.

In our country, India, the majority of patients with cancer sponsor their own treatment, a trend similar to many developing countries.[3,4] The cheapest generic variant of fulvestrant in the Indian market costs 11,500 in Indian national rupee (INR) ($156 in US dollars [USD]) for a dose of 250 mg. For a dose of 500 mg monthly, the cost of therapy is 23,000 (INR), which is more than double the national per capita income of 11,254 (INR) per month.[5] The ongoing COVID-19 pandemic also imposes insecurities for future earnings. In such a scenario, it makes sense to avoid a dogmatic view and critically look into the benefit derived from 500 mg fulvestrant compared with 250 mg. Would it be wise to use 250 mg fulvestrant? With the cost of cancer care pushing 60 million Indians below the poverty line every year,[6] a critical review of existing recommendations has the potential to stop the vicious cycle of poverty in cancer-afflicted families.

The need for sustained fulvestrant blood levels led to the development of the slow- and long-acting intramuscular preparations that are in use today. At a dose of 250 mg of long-acting intramuscular fulvestrant, an area under curve of 140.5 ng/mL was achieved after the first dose in healthy volunteers and steady-state levels were seen after three to six doses. The pharmacokinetic data also support continual accumulation of fulvestrant in the body with continuous dosing—in one of these studies, the mean trough concentrations of intramuscular fulvestrant were found to be 6.1 ng/mL after 6 months compared with 2.8 ng/mL after the first month.[7] Furthermore, there is no reason to assume that a flat dose of fulvestrant is adequate for all body weights—the average weight of an American woman is around 40% higher than an Indian woman.[8,9] Whether weight range will affect the drug levels is a subject that needs study. Patients with deranged liver function are treated with 250 mg fulvestrant.

Two randomized trials, FINDER1 and FINDER2, compared doses of 250 mg once a month approved dose (AD), 250 mg once a month with one loading dose (LD) of 500 mg, and 500 mg once a month high dose (HD) in patients with breast cancer. FINDER1 was conducted in Japanese patients and found response rates of 11.7%, 17.6%, and 10.6% in AD, LD, and HD, respectively.[10] FINDER2 was conducted in European and North American patients and found response rates of 8.5%, 5.9%, and 15.2% in AD, LD, and HD, respectively; however, the clinical benefit rate (CBR) was 47.1% and 47.8% in LD and HD, respectively. Thus, a higher dose provides a higher response rate in European and North American patients, although there is no impact on Japanese patients or on CBR. Time to progression was also similar in LD and HD.[11] The biomarker-driven neoadjuvant NEWEST trial randomly assigned patients between fulvestrant 500 mg once a month (with loading) and fulvestrant 250 mg once a month (without loading). Five hundred milligram of fulvestrant significantly decreased Ki67% and ER expression at d-28 as compared with 250 mg dose. However, the difference in the response rate (secondary outcome) of 22.9% *v* 20.6% was not statistically significant.[12,13] In the CONFIRM trial, 736 patients with de novo or recurrent advanced/metastatic HR-positive breast cancer were included and randomly assigned to fulvestrant 500 mg once a month (with loading) versus fulvestrant 250 mg once a month (without loading).[13,14] Patients with de novo metastatic disease who progressed on first-line therapy were 9.9% *v* 13.9% in 500 mg *v* 250 mg in the CONFIRM trial. The median overall survival (OS) benefit of 4.1 months led to regulatory approval of this schedule. However, it is important to note that this trial was designed for progression-free survival (PFS) benefit as primary end point not for OS.

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The difference in median PFS was only 1 month, 6.5 *v* 5.5 months (hazard ratio [HR], 0.8, $P < .01$). At the time of initial analysis,[13] the difference in median survival was only 2.3 months and was not statistically significant (HR, 0.84, $P = .091$). The subsequent analysis demonstrating a significant 4.1 month difference was statistically unsound, as it did not take into account multiplicity and no alpha was retained for this analysis after the previous study. In fact, the authors comment in the discussion that the survival benefit must be considered exploratory only.[14] Fulvestrant 500 mg was widely accepted as the international standard. A similar study conducted in 221 Chinese patients did not demonstrate a statistically significant PFS benefit (HR, 0.75, $P = .078$). Additionally, the study had high rates of censoring in predefined end points.[15,16] An important limitation across all these trials is the comparison of 500 mg dose (with loading) with 250 mg dose (without loading). Except for the FINDER studies, others have used the AD schedule as the control arm, which does not represent a fair comparison. Because of the statistical limitations of the final survival analysis of CONFIRM, it should be clear that the question of OS with 250 mg *v* 500 mg is by no means settled and remains open.

Cost-effectiveness of adding 250 mg fulvestrant to the treatment sequence of MBC was established in a 2008 study from the United Kingdom.[17] In a cost-effectiveness analysis conducted by Newman et al,[18] the incremental cost-effectiveness ratio as determined by the Markov model was $10,972 (USD) per month of progression-free survival for the 500 mg dose compared with the 250 mg dose, concluding that 250 mg of fulvestrant remains as a viable option for targeted settings where insurance coverage is not adequate. It should be noted that the above two studies are based on health systems in developing economies and not developing countries. Limited health insurance coverage[19] and the pandemic situation make this discussion more relevant and emphasize the importance of remembering the lessons of history.

Considering CBR at 24 weeks as a clinically meaningful end point, the difference in 24-week CBR between the two dosing schedules (250 mg *v* 500 mg) is 6% (45.6% *v* 39.6%).[13] This indicates a number needed to treat of 16 patients. Thus, treating 16 patients will enable one additional patient to be in remission at the 24-week mark. The cheapest brand of fulvestrant in India costs 11,500 (INR) per 250 mg. Assuming a median of seven doses per patient, the additional cost of achieving this outcome is 12,88,000 (INR) (11,500 × 16 patients × 7 doses). Keeping in mind a median PFS benefit of only 1 month, the implications are huge. A small retrospective study from India recently demonstrated no implication of fulvestrant dose on PFS, although the sample size is too small to detect an expected median PFS difference of 1 month.[20] As the COVID-19 pandemic hit the world economies,[21] many have foretold that it is a new normal of economic strain and entry into a new recession. It is thus a good time to take a relook into increased spending on interventions that produce small benefits to individual patients. Another reason to relook at the data is the development of new treatments that offer more substantial improvements in PFS and/or OS at higher cost-effectiveness. In an era before cyclin-dependent kinases antagonists, it might have been cost-effective (maybe for developed countries) to spend $10,972 (USD) per month on a therapy that improves median PFS by only 1 month. This situation definitely changes with the development of newer technologies, such as cyclin-dependent kinases antagonists. While consideration of all frontline recommendations is ethically correct, in the developing world, we often face a choice where to put our resources; in this scenario, treatments with small benefit at high cost should be cut out of national protocols. In this context, it is important to note that ASCO recommends a 500 mg dose of fulvestrant in its most recent guideline and does not mention 250 mg as an option.[22]

In conclusion, while the data support the superiority of a 500 mg dose of fulvestrant, the benefits offered are small in relation to the cost burden, and thus, this dose is not justified for routine use, at least as it applies to developing countries like India. We suggest that 250 mg monthly with a single LD of 500 mg can be used for the vast majority of patients, with 500 mg monthly reserved for patients with higher income. This small intervention can halve the cost of therapy for most of our patients while preserving most of the clinical benefits. Resource-limited countries or people with limited insurance or self-funded treatment may benefit from such approaches. Patient participation is encouraged while making balanced decisions in similar situations where narrow differences in clinical outcomes are associated with a large economic impact.

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